REMARKS

Formal Matters

Applicants thank the Examiner for reconsidering and removing the restriction requirement, based on Applicants' response filed July 29, 2004. *See* Office Action at page 2. The Examiner stated that claims 1-16 were under consideration for examination. *Id.* However, because Applicants' Supplemental Preliminary Amendment, filed November 26, 2002, was allegedly improper, the Examiner withdrew claims 1-16 as non-elected. *Id.* Further, the Examiner renumbered claims 1-16, as amended in Applicants' Supplemental Preliminary Amendment filed November 26, 2002, and entered these claims as claims 17-32. Applicants respectfully submit that the amendment filed November 26, 2002, was not improper. However, because claims 1-16, as amended, were merely renumbered, and to expedite prosecution, Applicants acknowledge that claims 17-32 are pending and have been examined in the Office Action mailed September 23, 2004. Applicants refer to these claims as "previously presented," because of their presentation in the Amendment filed November 26, 2002, and because the Examiner stated that the claims have been renumbered and claim dependencies corrected. *See* Office Action at page 2.

In the current response, Applicants have amended claims 17, 18, 22, and 24-27. No new matter has been added to the claims by way of these amendments. Applicants also canceled claims 23, 30 and 31.

Claims 17-22, 24-29, and 32 are now pending in this application.

Information Disclosure Statement

Applicants note that the Examiner did not consider the *Baba* reference (PTH/PTHrP, Clinical Calcium, 5:97-101 (1995)), cited in the Supplemental Information Disclosure Statement filed March 18, 2003. The *Baba* citation indicated that an English translation had been provided, yet the Examiner wrote "not translated" to the left the citation. Applicants provide an additional copy of the *Baba* reference and its English translation with this Office Action Response, as well as a clean copy of the originally provided form listing the document. Applicants respectfully request that the Examiner review this reference and indicate that it has been considered.

Objections to the Specification

The Examiner objected to the specification because "it contains references to figures on page 44 ('Fig. 5') and page 62 ('Fig. 7' and 'Fig. 8') that are not disclosed." Office Action at page 3. In addition, the Examiner objected to a grammatical error on page 21, second paragraph. *Id.* Applicants removed the references to Figures 5, 7, and 8 from the specification and corrected the grammatical error. Applicants therefore request that the Examiner withdraw these objections.

Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejected claims 17-32 under the judicially created doctrine of obviousness-type double patenting, stating that these claims are not patentably distinct over claims 1, 4, 6, 9-16, 19-21, and 33 of copending Application No. 09/720,326. Office Action at page 4.

Applicants will consider filing a terminal disclaimer to overcome these rejections once patentable subject matter has been indicated in this case. Until then, Applicants request that the Examiner hold the rejection in abeyance.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 17-32 were rejected by the Examiner because the specification allegedly does not reasonably provide enablement to make or use the present invention. *See* Office Action at pages 5-9. Specifically, claim 17 was rejected by the Examiner under 35 U.S.C. § 112 for reciting the term "preventing." Office Action at page 6. The Examiner stated that the specification fails "to meet the requirement for 'preventing' at least one symptom of drug-resistant hypercalcemia." *Id.* Applicants respectfully traverse. However, merely to expedite prosecution, Applicants have deleted the word "preventing" and amended claim 17 to read "A method for treating a patient suffering from or susceptible to at least one symptom of drug-resistant hypercalcemia." Applicants therefore respectfully request that the Examiner withdraw this enablement rejection of claim 17.

The Examiner also made the following three enablement rejections:

- Claims 17-32 were rejected because allegedly the term "substance" can encompass potentially thousands upon thousands of compounds. Office Action at page 6.
- Claims 22 and 30 were rejected because allegedly "[t]he specification fails to disclose the vast number of PTHrP antagonists that may or may have

the ability to operate within the framework of the present invention." Office Action at page 9.

- Claims 23-27 and 30-31 were rejected because allegedly "[t]he specification fails to disclose the vast number of anti-PTHrP antibodies that can be directed towards different regions of PTHrP, which may or may have the ability to operate within the framework of the present invention." *Id.*

Applicants respectfully traverse. Although Applicants believe that these concepts are supported by the specification, Applicants have replaced the word "substance" in claims 17, 18, and 22 with "anti-PTHrP antibody." Further, Applicants have canceled claim 23, 30, and 31, which do not further limit the claims as amended. Applicants reserve the right to pursue these claims in a separate application.

One of skill in the art would be able to make and use the claimed invention, as amended, using the teachings in the application as a guide:

- A description of antibodies and methods of making them is provided on pages 4-5 of the specification. A specific example of an antibody, #23-57-137-1, is also provided along with information regarding its deposit under Accession No. FERM BP-5631.
- The specification at pages 5-8 teaches how a monoclonal antibody-producing hybridoma can be prepared.
- The production of recombinant antibodies is taught at pages 8-10.

- The preparation of modified antibodies and fragments of antibodies is discussed at pages 12-13.
- Expression, production, isolation, and purification of recombinant or modified antibodies are detailed at pages 13-15.
- Determination of the binding activity and neutralizing activity of an antibody is taught at pages 15-16.
- Pages 16-17 describe routes of administration, dosage, and pharmaceutical preparations, including pharmaceutical carriers and additives.
- Examples 1-2 (specification at pages 18-23) teach administration of a humanized anti-PTHrP antibody to a model animal of hypercalcemia resistant to a biphosphonate or calcitonin. Examples 1-2 teach that administration of the antibody ameliorated increased blood calcium levels. *See* Figures 1 and 3.

One of ordinary skill in the art based on these teaching would be able to both make and use the anti-PTHrP antibodies of the invention. In light of the amendment to independent claim 17, and these arguments, Applicants request that the Examiner withdraw these three enablement rejections.

The Examiner rejected claims 18-32 because allegedly the only therapeutic agents disclosed are a "biphosphonate (Alendronate) and a calcitonin (Elcatonin), which fails to take into consideration the other potential therapeutic agents that may exhibit drug-resistant hypercalcemia." Office Action at page 7. Further, the Examiner stated that "[i]t is even conceivable that the present invention may at some point show drug-resistant hypercalcemia." *Id.* Applicants respectfully traverse.

The Examiner mistakes the possible need for some experimentation to mean that there is an utter lack of enabling disclosure supporting the full scope of the claimed invention. The *Wands* case cited by the Examiner explains:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.' "

In re Wands, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (footnote omitted) (quoting *In re Angstadt,* 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976)). Any experimentation needed to determine drug-resistance would not be undue. The specification notes that researchers have already identified two representative compounds, calcitonins and biphosphonates, that exhibit reduced efficacy (drug-resistance) after repeated administration. *See* specification at pages 1-2. Furthermore, Examples 1 and 2 demonstrate experimentally the progression of drug resistance after repeated administration of both alendronate (Example 1) and elcatonin (Example 2). Figures 1 and 3 show that blood calcium levels are initially decreased upon alendronate and elcatonin administration, respectively. However, after repeated administration the calcium levels increase significantly and are not affected by subsequent drug administration, i.e. drug-resistant hypercalcemia has developed. *See* Figures 1 and 3. PTHrP antibody administration was able to treat the drug-resistant hypercalcemia by decreasing blood calcium levels when alendronate and elcatonin administration were ineffective. *Id.* Finally, Applicants note that anti-PTHrP antibodies do not themselves attenuate in efficacy after repeated administration, which can be confirmed by routine testing. As *Wands* requires, any necessary experimentation to determine if drug-

resistance is created by a particular compound is routine and fully described in the specification. Therefore, Applicants respectfully request the Examiner to withdraw this enablement rejection.

Written Description Rejection

The Examiner rejected claims 17-18, 20 and 22-24 as lacking written description. Specifically, the Examiner was concerned regarding the phrase "at least one substance" in claim 17 and the phrase "an antagonist of the PTHrP receptor" in claim 22. Office Action at pages 10-11. Applicants respectfully disagree. Applicants note, as discussed above however, that claim 23 has been canceled without prejudice or disclaimer. Further, claims 17, 18, and 22 have been amended by replacing the word "substance" with the phrase "anti-PTHrP antibody." Applicants note that the Examiner stated that the specification adequately describes an antibody that is directed to the ligand. Office Action at page 11. Applicants therefore assert that the claims, as amended, fulfill the written description requirement and request that the Examiner withdraw this rejection.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 17-32, as being anticipated under 35 U.S.C. § 102(b) by Sato *et al.* (AU 199743972). The Examiner specifically asserts that "Sato *et al* teach that PTHrP is involved in hypercalcemia associated with malignancy and that repeated treatment using clacitonin, biphosphonate, etc. results in decreased efficacy, i.e. drug-resistant hypercalcemia, over time (p. 4 lines 14-23)." Office Action at page 12. Further, the Examiner states that "Sato et al. also teach that since drug-resistance

occurs as a result of repeated exposure to certain compounds a novel approach may be to use antibodies directed towards PTHrP." *Id.* Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P § 2131. Applicants respectfully submit that Sato *et al.* do not distinctly disclose the treatment of drug-resistant hypercalcemia. Sato *et al.* do describe progression of hypercalcemia to drug-resistant hypercalcemia after chronic administration of biphosphonates or calcitonins. *See* Sato *et al.*, page 4, lines 19-23. However, contrary to the Examiner's assertion, Sato *et al.* do not teach or suggest that PTHrP antibodies can be used to treat drug-resistant hypercalcemia once it has developed. The reference teaches that PTHrP antibodies can be used to treat hypercalcemia. *See, e.g.*, Examples 5-7, pages 111-116. However, when a patient develops drug-resistant hypercalcemia, administration of the drug will normally be discontinued. Thus, the therapeutic strategy for drug-resistant hypercalcemia is quite different than that for hypercalcemia. In summary, while Sato *et al.* discloses the effectiveness of PTHrP antibodies for the treatment of hypercalcemia, they do not disclose, and it is impossible to predict, whether or not the same antibody is effective in treating drug-resistant hyercalcemia. Sato *et al.* do not disclose the administration of a PTHrP antibody to treat drug-resistant hypercalcemia, as independent claim 17 recites. Additionally, not every hypercalcemia can be characterized as drug-resistant or even develops into a drug-resistant condition; treatment of drug-resistant hypercalcemia is not inherent in the

treatment of simple hypercalcemia. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Amy E. Purcell
Amy E. Purcell
Reg. No. 53,492